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Rapid and durable recovery of immune effector cells in myelofibrosis patients treated with momelotinib

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Running title: Immune Recovery with Momelotinib in Myelofibrosis

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Contributions:

PH conceived the study. JM, KHT, and PH developed the methodology. MP, CS, HdL, NC, PS, DHR, CW, BN, JS, and PH recruited study patients. JM, KHT, AS, LC, AD, ET, and PH collected and assembled the data. JM and PH performed data analysis, with input from all authors. JM, KHT, AS, BP, SK, CH, and PH contributed to the scientific discussion. JM and PH wrote the manuscript. PH supervised the study. All authors read and approved the final manuscript.

Data Availability Request:

Data that support the findings of this study are available from the corresponding author, [PH], upon reasonable request.

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Myelofibrosis is characterized by progressive bone marrow fibrosis and remodeling, with a resulting cascade of disrupted hematopoiesis, cytopenias, splenomegaly, and constitutional symptoms. Constitutive JAK-STAT activation underpins the efficacy of JAK inhibitors (JAKi) in myelofibrosis. Ruxolitinib, the first JAKi approved for myelofibrosis, revolutionized the treatment landscape of the disease. However, ruxolitinib is also significantly immunosuppressive, leading to impairment of natural killer (NK) cell function, dendritic cell activation, and T-cell responses, amongst other effects.¹⁻³ Consequently, infection rates and other complications secondary to chronic immunosuppression, such as second malignancies, particularly non-melanoma skin cancers, are significantly more common in ruxolitinib-treated patients.⁴⁻⁶ Among the newly approved JAKi, momelotinib is a JAK1/JAK2/ACVR1 inhibitor indicated in myelofibrosis patients with anemia.⁷

In a 'real-world' cohort of 46 patients on momelotinib, we collected sequential peripheral blood samples over a 48-week period to assess changes in immune cell frequencies and hematological response. Study patients were enrolled at our institution prospectively between July 2023 and February 2025. The study was approved by a formally constituted review board (REC reference: 23/NW/0105) and written consent was obtained from participants. Samples were collected, where available, at the time of momelotinib initiation, referred to as baseline from hereon, and at 6, 12, 24, and 48 weeks thereafter. Data from 10 healthy controls (HC) were used as a comparator (median age: 60 years [52-77 years]; males n=7, females n=3). Whole blood samples were analyzed via flow cytometry using Aquios Tetra 1 and 2 antibody combinations (Beckman Coulter, U.S.A.) to detect absolute counts for CD45+ cells, CD3+ cells, CD3+CD4+ cells, CD3+CD8+ cells, CD3-CD19+ cells, and CD3-CD56+/CD16+ cells. For normally distributed data, as determined by the Shapiro-Wilk test, t-tests and one-way ANOVA were used; otherwise, Mann-Whitney U and Kruskal-Wallis tests were used. Statistical analyses were performed using Python 3.11.6 with SciPy (version 1.15.2) and Statsmodels (version 0.14.4).

Cohort demographics are detailed in Supplementary Table 1. Briefly, 46 patients were included. 18 patients had primary and 28 secondary myelofibrosis. As per DIPSS+ classification, 16 patients were high-risk, 24 intermediate-risk 2, and 6 intermediate-risk 1. Of these, 36 received momelotinib at a daily dose of 200 mg (1 started at 150 mg and escalated to 200mg); others were on a reduced dose. The median age at momelotinib commencement was 70.5 years [47-83 years] (males n=27, females n=19). 39/46 (85%) patients had prior ruxolitinib exposure (median time: 1.5 years), with 35 discontinuing due to anemia. 30 patients transitioned directly from ruxolitinib to momelotinib within 4 weeks, with the majority of these transitioning directly the following day without a washout period as per routine clinical practice. 4 patients were on concurrent hydroxycarbamide (n=1 throughout, n=2 from 12 weeks, n=1 from 24 weeks).

At baseline, patients had significantly lower frequencies of total lymphocytes, CD3+ and CD4+ T cells, and NK cells compared to HC (1041 versus 1557, 724 versus 1085.5, 476 versus 716, and 92 versus 216.5 cells/µL respectively; p=0.03, 0.01, 0.005, and 0.004 respectively) (Table 1, Figure 1A).

T-cell subsets increased by week 6, returning towards levels observed in HC. CD3+ counts were 968, 1112, 876, and 1082 cells/µL at 6 weeks (6w), 12 weeks (12w), 24

weeks (24w), and 48 weeks (48w) respectively. CD4+ T-cell counts were 552.5, 714, 486, and 721, while CD8+ were 324, 368, 316, and 316 cells/ μ L, respectively. These frequencies were significantly higher than baseline at most time points (p-values for CD3+: 0.01, <0.01, 0.08, 0.03; CD4+: 0.03, 0.02, 0.19, 0.03; and CD8+: 0.04, 0.05, 0.28, 0.13, respectively).

The recovery of NK cells was the most pronounced and persistent, increasing from 92 cells/ μ L at baseline to 202 (6w), 197 (12w), 162 (24w), and 270.5 (48w) cells/ μ L (p <0.01, <0.01, 0.01, and <0.01, respectively). NK cell frequencies on momelotinib remained comparable to HC: p=0.64 (6w), 0.93 (12w), 0.72 (24w), and 0.47 (48w).

The B-cell counts at baseline were comparable to those of HC, with median values of 176 and 201.5 cells/ μ L, respectively (p=0.54). Their counts increased at 6 weeks (289.5 cells/ μ L) and remained elevated (225, 180, and 277 cells/ μ L at 12, 24, and 48 weeks). This increase was significant at week 6 (p=0.02) and 48 (p=0.04); however, B-cell counts did not differ significantly from HC at any time point.

Interestingly, in 4/5 patients without prior ruxolitinib exposure, we also observed an upward trend in all lymphocyte subsets. The fifth patient showed an initial increase from baseline to 12 weeks, followed by a decline to baseline levels at 24 weeks, with no obvious explanation. Overall, for these 5 patients, median total lymphocyte counts were 732.5 cells/ μ L at baseline, which subsequently increased to 903 (6w), 1398 (12w), 1385.5 (24w) and 1581 cells/ μ L (48w), CD3+ cells were: 523, 620, 1002.5, 897, and 1024, CD4+ T cells were: 375.5, 299, 709.5, 602.5, and 723.5, CD8+ T cells were: 139.5, 189, 360.5, 267, and 315, NK were: 145.5, 141, 208.5, 443, and 383, and B cells were: 62, 82, 158.5, 120.5, and 108.5 cells/ μ L at baseline, 6w, 12w, 24w, and 48w, respectively (Supplementary Table 2). A similar trend was observed in all six patients with remote ruxolitinib exposure (\geq 4 weeks preceding momelotinib initiation), with no significant differences from those with recent exposure (< 4 weeks) (Supplementary Table 2).

Further subgroup analyses also revealed no significant differences in immune subset frequencies between patients with primary versus secondary myelofibrosis, different DIPSS+ categories, distinct driver mutations, presence of additional high-risk mutations, previous ruxolitinib dosage, or momelotinib dosing regimen.

Consistent with previous reports, we also observed a significant hematological response in our cohort (**Figures 1B and 1C**).⁸⁻¹⁰ At baseline, 22% (n=10/45) of patients were transfusion-dependent (requiring \geq 6 red blood cell transfusions in the preceding 12 weeks), while 17 were transfusion-independent. The remaining 40% (n=18) received occasional transfusions. By 12 weeks, only 4 patients remained transfusion-dependent, whereas 27/43 achieved transfusion independence (TI), which was largely maintained until their follow-up (24w: n=22/24; 48w: n=13/14). Eight additional patients gained TI at 24w and 1 further at 48w. 2/5 patients with advanced-stage chronic kidney disease (Stage IIIb, IV) also achieved TI. In the TI cases, median hemoglobin increased from a baseline of 91 g/L (n=17) to 102 g/L at 12w (n=27, p=0.02), with this improvement sustained at subsequent timepoints (24w: hemoglobin=105 g/L, p=0.01, n=29; 48w: hemoglobin=108.5 g/L, p=0.03, n=16) (Figure 1B and 1C).

Overall, momelotinib was well-tolerated in our cohort. Patients demonstrated a striking improvement in their immune cell populations as early as 6 weeks, which persisted until at least 48 weeks on momelotinib. Importantly, these effects were observed not only in patients previously treated with ruxolitinib but also in ruxolitinib-naïve individuals and in those with remote exposure, suggesting an independent immunomodulatory effect of momelotinib beyond mere ruxolitinib withdrawal.

The reconstitution of T and NK cells is particularly relevant given their pivotal roles in pathogen clearance, vaccine responses, and tumor surveillance.^{3,11} Notably, ruxolitinib has markedly lower IC₅₀ for both JAK1 and JAK2 when compared with momelotinib.¹² Ruxolitinib has been demonstrated to have an IC₅₀ of 3.2 nM for JAK2 compared with 11 nM for momelotinib in the presence of physiologic ATP (1 mM), in one analysis.¹² This heightened inhibition of JAK1 and JAK2 signaling, which is central to the cellular function of both T and NK cells, may underpin some of the effects we have observed. In vitro phosphoflow analysis has also demonstrated variable inhibition of different JAK-STAT signalling pathways among different JAK inhibitors.¹³

In addition, different JAK inhibitors have been demonstrated to have diverging immunological activity, suggesting inhibitory effects beyond JAK-STAT and ACVR1 inhibition.¹⁴ Using a panel of human cell system profiles to determine biomarker activity, JAK inhibitors, at clinically relevant concentrations, differentially modulated inflammatory cytokine production and immune function, with ruxolitinib showing the broadest scope of inhibition across all systems evaluated.¹⁴ The absence of differences in B cell frequencies relative to HC is consistent with previous findings in healthy donor PBMCs, where neither ruxolitinib nor momelotinib significantly affected B-cell proliferation, immunoglobulin production, or differentiation.¹⁵

In a large real-world cohort, the cumulative incidence of non-melanoma skin cancers after starting ruxolitinib was approximately 11.4% at a median follow-up of 2.9 years⁶, compared with 4.8% with momelotinib with a median follow-up of 11.3 months.¹⁰ In SIMPLIFY-1, the rate of grade ≥ 3 infections was higher with momelotinib than with ruxolitinib (7% vs 3%), but lower in MOMENTUM (3% with momelotinib).^{8,10} However, when data from major studies was pooled, the overall infection incidence did not increase over time, rather, exposure-adjusted event rates for infections declined substantially during the open-label or extended treatment phase from 155.3 to 74.0 events per 100 person-years, suggesting possible attenuation of infection risk with prolonged therapy.¹⁰

Limitations of the study include the single-center nature of the patient cohort and intermittent data gaps inherent to real-world datasets, thus our findings require further validation. Nonetheless, the observed immune recovery in both JAKi-naïve and previously exposed patients across serial time points appears highly promising and may have significant implications in the selection of JAKi for myelofibrosis patients. Differential JAK1/JAK2 and off-target kinase inhibition may collectively contribute to momelotinib's distinct immunomodulatory effects.

Whether this quantitative preservation of cell-mediated immunity with momelotinib confers functional competence, reflected by a reduction in incidence and nature of infectious complications, decreased cancer risk, and sustained response to vaccines

remains to be established through systematic characterization over extended follow-up. Further mechanistic studies are also warranted to elucidate how these processes are mediated among all novel JAKi.

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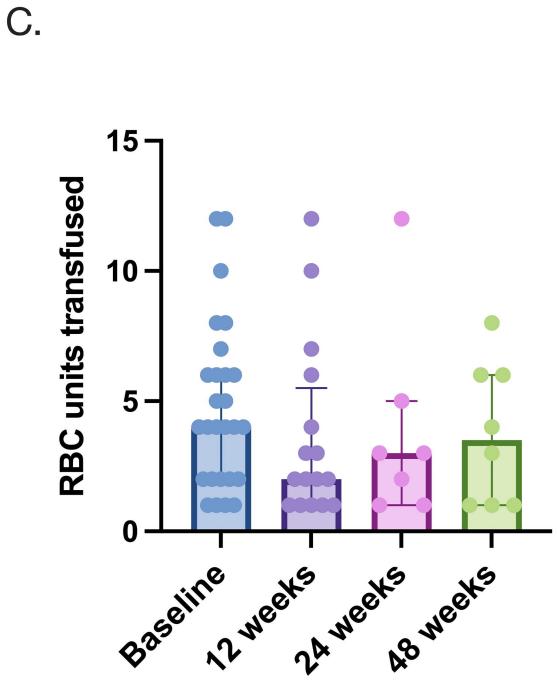
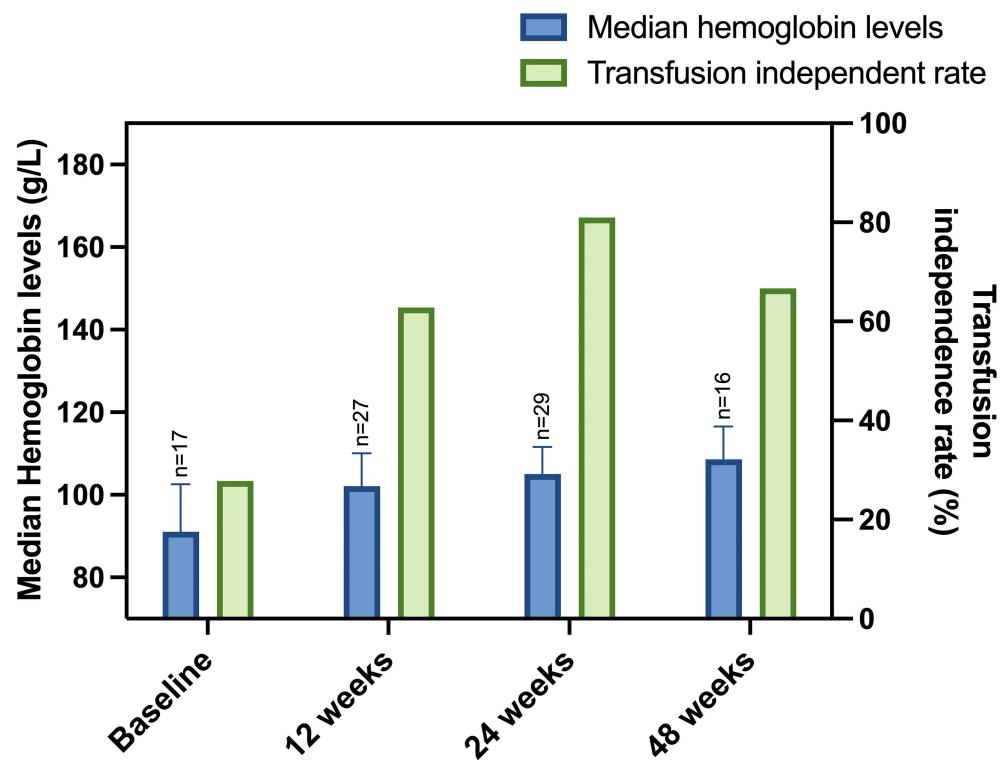
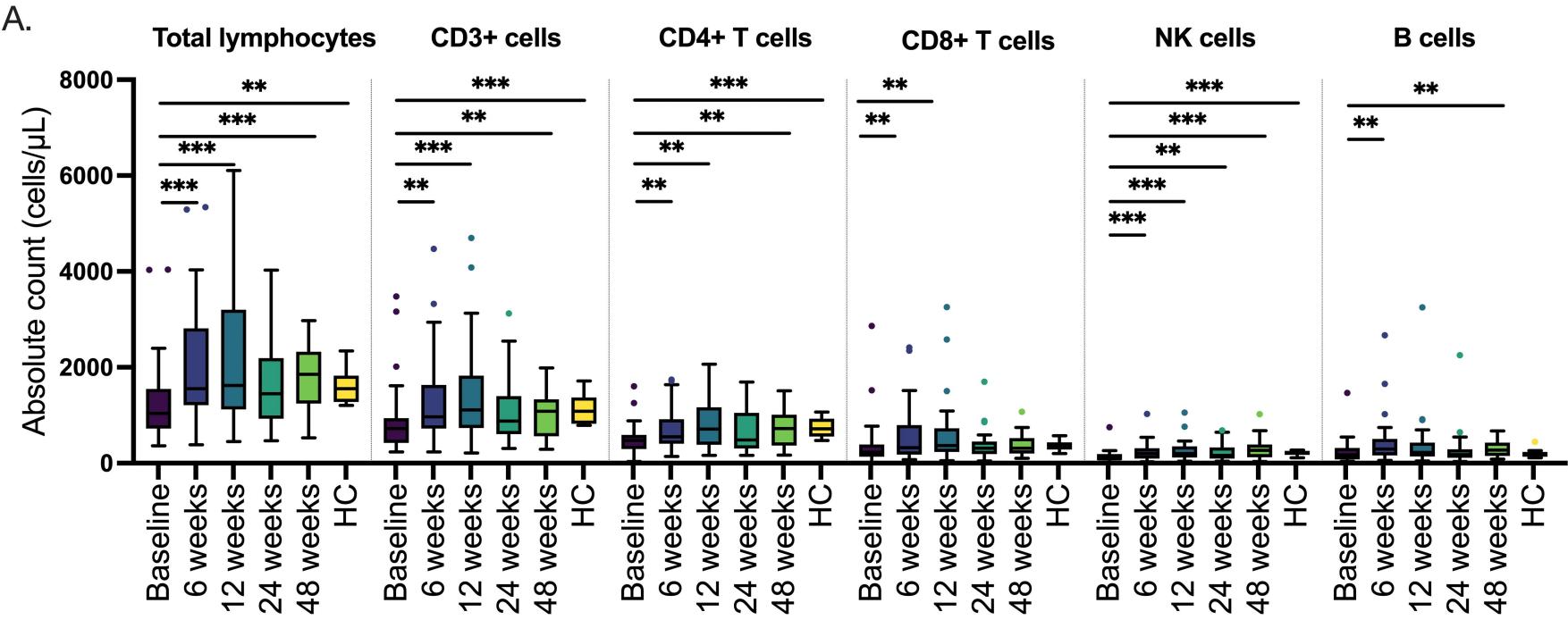
Table 1. Medians and interquartile ranges of immune cell subset levels at each time point for the entire patient cohort alongside healthy controls (HC). All cell numbers are expressed in cells/µL. Lab reference ranges for each subset, sample sizes (n), and p-values denoting the significance of difference relative to baseline are also included.

Immune subset (Reference ranges)	Baseline	6 weeks	12 weeks	24 weeks	48 weeks	HC
Total lymphocytes	1041 (738-1544) n=33	1556.5 (1263.8-2657.8) n=34 p=0.005	1623 (1191-2877) n=25 p=0.008	1450 (1031-2156) n=27 p=0.07	1857 (1322.3-2249.3) n=20 p=0.009	1557 (1300-1785.3) n=10 p=0.03
CD3+ cells (700-2100)	724 (454-923) n=33	968 (737-1598.5) n=34 p=0.01	1112 (736-1696) n=25 p=0.005	876 (625.5-1366.5) n=27 p=0.08	1082 (744-1327.5) n=19 p=0.03	1085.5 (867.3-1348.8) n=10 p=0.01
CD4+ T cells (300-1400)	476 (299-537) n=33	552.5 (416-896.3) n=34 p=0.03	714 (413-1093) n=25 p=0.02	486 (351.5-1025.5) n=27 p=0.19	721 (456.3-952.5) n=20 p=0.03	716 (579-903.8) n=10 p=0.005
CD8+ T cells (200-900)	229 (138-393) n=33	324 (186-787) n=34 p=0.04	368 (265-621) n=25 p=0.05	316 (192-446.5) n=27 p=0.28	316 (203.3-466.5) n=20 p=0.13	379.5 (317.5-416.8) n=10 p=0.07
NK cells (90-600)	92 (61-176) n=33	204.5 (100.8-306) n=34 p=0.005	202 (121-332) n=25 p=0.001	162 (97.5-313) n=27 p=0.01	270.5 (140-392) n=20 p=0.002	216.5 (185-252.5) n=10 p=0.004
B cells (100-500)	176 (83.5-301.3) n=32	289.5 (165-494.5) n=34 p=0.02	225 (147-425) n=25 p=0.12	180 (125.5-289) n=27 p=0.46	277 (157.5-419.5) n=19 p=0.04	201.5 (141.5-222.8) n=10 p=0.54

Figure 1.

Immune and haematologic response to momelotinib treatment

A. Immune subset frequencies (cells/ μ L) at each time point are presented alongside healthy controls with median, interquartile ranges, full ranges, and outliers (defined as values beyond $\pm 1.5 \times \text{IQR}$). B. Hemoglobin levels (median, IQR, and number of individuals) in transfusion-independent patients and proportion of all patients that are transfusion-independent at each time point. C. Number of RBC units transfused (median, IQR, and outliers) in patients still requiring transfusions.



Supplementary Table 1. Cohort demographics

Variable	Frequency	Median (IQR)
Age		70.5 years (66.3-75.8)
Gender: female, male	19, 27	
Diagnosis		
<i>Primary MF</i>	18	
<i>PET-MF</i>	20	
<i>PPV-MF</i>	7	
<i>MPNu-MF</i>	1	
DIPSS+ score		
<i>High</i>	16	
<i>IR2</i>	24	
<i>IR1</i>	6	
JAKi exposure	39	
<i>Ruxolitinib</i>	39	
<i>Fedratinib</i>	1	
Ruxolitinib dosage		
<i>High (≥25 mg daily)</i>	17	
<i>Low (<25 mg daily)</i>	20	
<i>Unknown</i>	1	
Time on ruxolitinib		1.5 years (0.5-3)
Reason for ruxolitinib discontinuation		
<i>Anemia</i>	35	
<i>Thrombocytopenia</i>	3	
<i>Other</i>	2	
Direct ruxolitinib-to-momelotinib transition interval	38	
<i>≥4 weeks</i>	8	
<i><4 weeks</i>	30	
Momelotinib dose		
<i>200mg OD</i>	35	
<i>150mg OD → 200mg</i>	1	
<i>200mg OD → 100mg</i>	2	
<i>200mg alt days</i>	1	
<i>150mg OD</i>	1	
<i>100mg OD</i>	6	
Reason for momelotinib dose reduction		
<i>Poor renal function</i>	5	
<i>Thrombocytopenia</i>	2	
<i>Frailty</i>	1	
<i>Fatigue</i>	1	
<i>Unknown</i>	1	
Chronic kidney disease stage		
<i>4</i>	2	
<i>3b</i>	5	
<i>3a</i>	12	

Baseline driver mutations			
	JAK2	28	
	CALR	10	
	MPL	7	

Supplementary Table 2. Medians and interquartile range of immune cell subset levels at each time point stratified by analyzed subgroups. All cell counts are expressed in cells/ μ L. Lab reference ranges and sample sizes (n) at each time point are included.

Immune subset (Reference ranges)	Baseline	6 weeks	12 weeks	24 weeks	48 weeks
RUX-naïve vs. RUX exposed					
Total lymphocytes	732.5 (484.8-1722); n=4 vs. 1124 (801-1544); n=29	903 (707.5-1181); n=3 vs. 1576 (1298.5-2835); n=31	1398 (1155.8-2729.8); n=4 vs. 1738 (1295-2877); n=21	1385.5 (1240.3-2129); n=4 vs. 1450 (915.5-2156); n=23	1581 (982-2180); n=2 vs. 1797 (1283.5-2288.5); n=19
CD3+ cells (700-2100)	523 (372.25-1276.25); n=4 vs. 727 (498-923); n=29	620 (509-778); n=3 vs. 1050 (748-1655); n=31	1002.5 (846-2016); n=4 vs. 1112 (736-1696); n=21	897 (792.8-1484.8); n=4 vs. 876 (573.5-1366.5); n=23	1024 (714-1334); n=2 vs. 1069 (654-1310.3); n=18
CD4+ cells (300-1400)	375.5 (220.3-784.8); n=4 vs. 476 (361-537); n=29	299 (255.5-515.5); n=3 vs. 571 (436.5-926.5); n=31	709.5 (486.3-1171.8); n=4 vs. 714 (413-1093); n=21	602.5 (467.8-922.8); n=4 vs. 463 (300.5-1025.5); n=23	723.5 (403-1044); n=2 vs. 672 (413.5-898.5); n=19
CD8+ cells (200-900)	139.5 (137-486.8); n=4 vs. 232 (139-393); n=29	189 (169-256.6); n=3 vs. 368 (212.5-798.5); n=31	360.5 (316.3-921); n=4 vs. 375 (265-621); n=21	267 (212-662); n=4 vs. 334 (181-446.5); n=23	315 (295-335); n=2 vs. 332 (202.5-494); n=19
NK cells (90-600)	145.5 (70.8-350.3); n=4 vs. 92 (61-173); n=29	141 (99-233); n=3 vs. 207 (102.5-300); n=31	208.5 (133.3-460.3); n=4 vs. 202 (121-332); n=21	443 (266.5-567); n=4 vs. 152 (97.5-275); n=23	383 (131-635); n=2 vs. 270 (132-386); n=19
B cells (100-500)	62 (55-72); n=3 vs. 184 (95-329); n=29	82 (66-122); n=3 vs. 324 (178-507); n=31	158.5 (139-172.5); n=4 vs. 257 (177-432); n=21	120.5 (79.5-151.8); n=4 vs. 248 (141-297); n=23	108.5 (70-147); n=2 vs. 294.5 (167.3-424.3); n=18
Remote vs. recent RUX exposure					
Total lymphocytes	1183 (835-1668); n=5 vs. 1124 (848-1501); n=23	1397 (1009.25-2526.5); n=6 vs. 1753 (1326.8-2462.3); n=24	2877 (1393-3528); n=5 vs. 1680.5 (1190.8-2358.8); n=16	1393 (1362-1848.5); n=3 vs. 1621 (915.5-2156); n=19	1727 (1600.5-1853.5); n=2 vs. 1857 (1288.3-2376.3); n=16

CD3+ cells (700-2100)	687 (572-1042); n=5 vs. 751 (482.5-888.5); n=23	824 (652.5-2008); n=6 vs. 1093 (776.8-1593); n=24	1656 (876-3098); n=5 vs. 1111 (722-1598.5); n=16	876 (820.5-1138.5); n=3 vs. 999 (573.5-1387.5); n=19	977 (950.5-1003.5); n=2 vs. 1088 (777.5-1416.5); n=15
CD4+ cells (300-1400)	503 (294-537); n=5 vs. 476 (370-584); n=23	523 (343-1262.5); n=6 vs. 577 (439.3-919.3); n=24	1242 (456-1404); n=5 vs. 699.5 (399.3-904.3); n=16	456 (438.5-762); n=3 vs. 617 (300.5-1025.5); n=19	634.5 (566.8-702.3); n=2 vs. 732 (468-966.8); n=16
CD8+ cells (200-900)	244 (140-593); n=5 vs. 232 (146-384); n=23	324 (209.3-721.5); n=6 vs. 405 (241.5-777.75); n=24	375 (368-915); n=5 vs. 360.5 (229.5-594.75); n=16	334 (309-354.5); n=3 vs. 353 (181-474); n=19	281 (242.5-319.5); n=2 vs. 354.5 (208.5-556.3); n=16
NK cells (90-600)	160 (114-206); n=5 vs. 87 (55-138.5); n=23	219.5 (157.5-244.8); n=6 vs. 174.5 (104.3-314.5); n=24	266 (188-293); n=5 vs. 197 (119.3-349.8); n=16	266 (186-280); n=3 vs. 152 (87-275); n=19	396.5 (394.3-398.8); n=2 vs. 192.5 (109.5-326); n=16
B cells (100-500)	178.5 (92.3-315.3); n=4 vs. 184 (128-331); n=23	311 (175-511.5); n=6 vs. 312 (203.5-502); n=24	274 (180-534); n=5 vs. 243 (160.8-426.8); n=16	493 (336.5-570); n=3 vs. 242 (125.5-289); n=19	388.5 (281.3-495.8); n=2 vs. 277 (157.5-419.5); n=15

Supplementary Figure 1. Percentage change in spleen volume from baseline over time. Median, IQR, and number of observations are shown.

